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ORIGINAL ARTICLE

Impact of pre-infarction angina on angiographic and echocardiographic outcomes in patients with acute anterior wall myocardial infarction managed by primary percutaneous coronary intervention



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KEYWORDS

Pre-infarction angina;
Primary PCI;
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Abstract *Objectives:* To assess the impact of angina prior to first attack of acute anterior wall ST-segment elevation myocardial infarction (STEMI) on immediate angiographic and echocardiographic outcomes after primary percutaneous coronary intervention (PPCI).

Methods: A total of 100 patients with acute anterior wall STEMI managed by PPCI were included (50 patients with pre-infarction angina (PIA) and 50 patients without). Patients were observed for angiographic outcome (coronary collateral grade, final TIMI and TMP flow grade) and echocardiographic outcome.

Results: Baseline patient characteristics were similar in both groups. PIA group had more patients with grade 3 coronary collaterals ($p = 0.006$), more patients with TIMI 3 flow grade after PPCI ($p = 0.0002$), less patients with TMP 0 flow grade ($p = 0.013$). The group with no PIA had more advanced Killip class at presentation ($p = 0.015$).

No difference was present between both groups regarding post-PPCI LV ejection fraction ($p = 0.255$), LV end diastolic dimensions ($p = 0.553$), LV end systolic dimensions ($p = 0.908$), segmental wall motion score index ($p = 0.214$).

Conclusions: For patients suffering from a first attack of acute anterior wall STEMI, pre-infarction angina is associated with a better Killip class at presentation, better TIMI flow grade after PPCI, less incidence of TMP 0 flow grade.

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1. Introduction

Patients who suffer acute myocardial infarction (AMI) frequently experience prodromal symptoms preceding the attack itself known as pre-infarction angina (PIA). The clinical significance of PIA remains controversial. Studies have

demonstrated that such patients may have a smaller infarct size and better in-hospital outcome after AMI. This protective effect has been attributed to ischemic preconditioning, earlier reperfusion or better collateral circulation development.^{1,2}

Preconditioning is the process by which brief, repetitive episodes of ischemia reduce the size of a subsequent myocardial infarction.³ Several experimental and clinical studies reported improved outcome in AMI patients who experience pre-infarction angina who appeared to have decreased mortality, pump failure, arrhythmias, and peak cardiac serum enzyme levels as well as enhanced recovery of cardiac contractile function.⁴⁻⁷

Studies have shown that PIA was associated with better 5-year clinical outcomes in STEMI patients undergoing primary PCI.⁸

The aim of this study was to assess the impact of pre-infarction angina prior to first attack of acute anterior wall ST-segment elevation myocardial infarction (STEMI) on angiographic and echocardiographic outcomes after primary percutaneous coronary intervention (PPCI).

2. Materials and methods

2.1. Study design

We conducted a prospective study of 100 patients presenting with first attack of acute anterior wall STEMI who were managed by PPCI.

MI was defined using the third universal definition of MI as the detection of a rise and/or fall of cardiac biomarkers, with at least one of the values being elevated (>99 th percentile upper reference limit) (using cardiac Troponin in this study), in addition to one of the five following predefined criteria: (1) symptoms of myocardial ischemia; (2) new (or presumably new) significant ST-segment/T-wave changes or left bundle branch block; (3) development of pathological Q waves on ECG; (4) new loss of viable myocardium or regional wall motion abnormality by imaging; and (5) identification of intracoronary thrombus by angiography or autopsy.⁹

Patients were excluded from the study for any of the following reasons: presenting more than 24 h after onset of chest pain, receiving fibrinolytic therapy, history of previous MI or acute coronary syndrome, history of chronic stable angina, STEMI in a territory other than the anterior wall, undergoing PPCI without stenting, chronic kidney disease requiring regular dialysis.

2.2. Patient groups

We assigned patients into two groups according to the presence or absence of pre-infarction angina (PIA) defined as the occurrence of attacks of typical transient ischemic-type chest pain (lasting less than 30 min) within the 24 h prior to developing MI; we enrolled 50 consecutive patients in each group. Approval of institutional ethical committee was obtained as well as an informed consent from each patient.

All patients received aspirin (300 mg PO) and clopidogrel (600 mg PO) in the emergency room. A detailed history and clinical examination were performed with particular

assessment of occurrence of PIA, presence of cardiac risk factors including smoking (current, regular use of any amount of tobacco or stopped less than 6 months ago), presence of hypertension (receiving hypertension treatment or blood pressure $>140/90$ mmHg), diabetes mellitus (receiving treatment for hyperglycemia), family history of premature atherosclerotic coronary artery disease (first degree relative with diagnosed CAD <60 years old). Also, Pain-to-door time was assessed as the time from onset of persistent chest pain to first medical contact.

2.3. Angiographic measurements

Coronary angiography was performed from the right femoral artery access site. Right coronary angiography was done first using a diagnostic catheter after which left coronary angiography in multiple orthogonal views was done using a guiding catheter. Patients underwent PPCI according to the current standards with stenting to the left anterior descending (LAD) artery using bare metal stents (BMS). Thrombus aspiration was not performed in any of the patients. A single run of balloon angioplasty was allowed using an undersized balloon (maximum 2.0 mm in diameter) inflated at nominal pressure after which stenting was performed. Glycoprotein IIb/IIIa antagonists were not administered during or after the procedure.

Coronary collateral grade to the LAD was assessed prior to PPCI. Both final Thrombolysis In Myocardial Infarction (TIMI) flow grade and Thrombolysis in Myocardial Infarction myocardial perfusion (TMP) grade were assessed after PPCI was done.

Final TIMI flow grade was classified as **TIMI 3** for normal antegrade flow and contrast clearance from the epicardial artery beyond the (stented) obstruction (complete perfusion); **TIMI 2** for full opacification of the distal artery, but with slower contrast flow or clearance, or both, beyond the (stented) obstruction compared with a non-culprit artery or the culprit artery proximal to the lesion (partial reperfusion); **TIMI 1** for contrast flow in part, but not all, of the artery distal to the (stented) obstruction (penetration without perfusion); **TIMI 0** for no antegrade contrast flow beyond the point of occlusion (no perfusion).¹⁰

Final TMP grade was classified as **TMP grade 3** when there was the normal diffuse ground glass appearance of myocardial blush so that at the end of the washout phase, dye was only mildly persistent or gone; **TMP grade 2** when dye entered the myocardium, but accumulated and exited more slowly, so that at the end of the washout phase dye in the myocardium was strongly persistent; however, dye totally cleared by the next injection; **TMP grade 1** when the dye did not leave the myocardium and there was a stain on the next injection; **TMP grade 0** when dye did not enter the myocardium and there was minimal or no blush apparent during the injection and washout phases.¹¹

Grades of coronary collaterals were classified according to Rentrop as **Grade 0** for no collaterals; **Grade 1** for filling of side branches of the artery to be perfused via collateral vessels without visualization of the epicardial segment; **Grade 2** for partial filling of the epicardial segment via collateral vessels; **Grade 3** for complete filling of the epicardial segment via collateral vessels.¹²

2.4. Echocardiographic measurements

A full trans-thoracic echocardiography study was performed for all patients on the morning after PPCI using a General Electric S5 echocardiography machine with a 2.5 MHz phased array transducer with the patient lying in the left lateral decubitus position. All examinations were done by an experienced echocardiographer who was blinded to the patients' group.

The following measurements were obtained: Left ventricular (LV) dimensions, left ventricular ejection fraction (LVEF) assessed using the modified Simpson method of discs, mitral regurgitation grade, and the segmental wall motion score index according to the 16-segment model described by the American Society of Echocardiography.¹³

2.5. Comparing outcome

Both groups were compared regarding:

- A. Angiographic outcome after revascularization: (1) Final TIMI flow grade in the LAD. (2) Final TMP grade in the LAD territory.
- B. Echocardiographic outcome: LV dimensions, LVEF assessed by the modified Simpson method of discs and segmental wall motion score index.

2.6. Statistical analysis

Data were coded, tabulated, and statistically analyzed using Graph Pad Prism software. Descriptive statistics were done for continuous variables as mean \pm standard deviation, while they were done for categorical variables as number and percentage. Tests performed were 2-tailed Student *t*-test and Fisher's exact test. The level of significance was taken at *p* value less than 0.05, otherwise was considered non-significant.

3. Results

Our study included 100 patients (from April 2013 to March 2014) classified into two equal groups: PIA group represents patients with history of pre-infarction angina (*n* = 50) and no-PIA group represents patients without history of pre-infarction angina (*n* = 50). All patients survived the PPCI procedure, 2 (2%) died in-hospital and the remaining 98 (98%) were healthily discharged from the hospital.

3.1. Baseline clinical characteristics

The 2 study groups were balanced as regards age, gender and cardiac risk factors (smoking, presence of hypertension, diabetes mellitus (type 2 in all), family history of premature atherosclerotic coronary artery disease). Pain-to-door time (from onset of persistent chest pain to first medical contact) was slightly shorter in the PIA group but not statistically significant (Table 1).

Regarding Killip class at presentation, more patients of the PIA group were in class 1 (92% vs. 70%, *p* = 0.009), while more of the no-PIA group were in class 4 (24% vs. 4%, *p* = 0.015) (Table 1).

Table 1 Baseline characteristics.

| Clinical characteristic | PIA group <i>n</i> = 50 | No PIA group <i>n</i> = 50 | <i>p</i> -value |
|---------------------------|----------------------------|-------------------------------|-----------------|
| Age, years | 56.5 \pm 12.2 | 55.9 \pm 10.5 | 0.839 |
| Male gender | 46 (92%) | 40 (80%) | 0.148 |
| Smoking | 36 (72%) | 31 (62%) | 0.395 |
| Hypertension | 13 (26%) | 13 (26%) | 1.18 |
| Diabetes mellitus | 16 (32%) | 15 (30%) | 1 |
| Positive FH of CAD | 3 (6%) | 3 (6%) | 1.322 |
| <i>Killip class</i> | | | |
| 1 | 46 (92%) | 35 (70%) | 0.009 |
| 2 | 2 (4%) | 3 (6%) | 1 |
| 3 | 0 (0%) | 1 (2%) | 1 |
| 4 | 2 (4%) | 11 (22%) | 0.015 |
| Pain-to-door time (hours) | 5.7 \pm 4.4 | 7.5 \pm 7 | 0.232 |

Continuous variables are expressed as mean and standard deviation; whereas categorical variables are expressed as numbers (percentage).

FH of CAD indicates family history of premature atherosclerotic coronary artery disease; PIA indicates pre-infarction angina.

3.2. Baseline coronary collateral grade prior to PPCI

The coronary collaterals grade of the whole cohort was: Rentrop grade 0 collaterals in 61 patients (61%), Rentrop grade 1 collaterals in 19 patients (19%), Rentrop grade 2 collaterals in 12 patients (12%) and Rentrop grade 3 collaterals in 8 patients (8%).

There were more patients with coronary grade 3 collaterals in the PIA group (16% vs. 0%, *p* = 0.006) and less with coronary grade 0 collaterals (44% vs. 78%, *p* = 0.0009) (Table 2).

Table 2 Baseline coronary collateral grade before PPCI and immediate angiographic outcome.

| Angiographic finding | PIA group <i>n</i> = 50 | No PIA group <i>n</i> = 50 | <i>p</i> -value |
|----------------------------------|----------------------------|-------------------------------|-----------------|
| <i>Coronary collateral grade</i> | | | |
| Rentrop grade 0 | 22 (44%) | 39 (78%) | 0.0009 |
| Rentrop grade 1 | 13 (26%) | 6 (12%) | 0.125 |
| Rentrop grade 2 | 7 (14%) | 5 (10%) | 0.759 |
| Rentrop grade 3 | 8 (16%) | 0 (0%) | 0.006 |
| <i>Final TIMI flow grade</i> | | | |
| TIMI 0 | 0 (0%) | 2 (4%) | 0.495 |
| TIMI 1 | 0 (0%) | 7 (14%) | 0.013 |
| TIMI 2 | 2 (4%) | 8 (16%) | 0.091 |
| TIMI 3 | 48 (96%) | 33 (66%) | 0.0002 |
| <i>Final TMP grade</i> | | | |
| TMP 0 | 0 (0%) | 7 (14%) | 0.013 |
| TMP 1 | 3 (6%) | 2 (4%) | 1 |
| TMP 2 | 9 (18%) | 11 (22%) | 0.803 |
| TMP 3 | 38 (76%) | 30 (60%) | 0.133 |

Categorical variables are expressed numbers (percentage).

PIA indicates pre-infarction angina; TIMI indicates Thrombolysis In Myocardial Infarction; TMP indicates Thrombolysis In Myocardial Infarction myocardial perfusion.

Table 3 Echocardiographic outcome.

| Outcome | PIA group <i>n</i> = 50 | No PIA group <i>n</i> = 50 | <i>p</i> -value |
|---|----------------------------|-------------------------------|-----------------|
| <i>General echocardiographic outcome</i> | | | |
| LVEDD (mm) | 53.4 ± 7.6 | 54.2 ± 5.7 | 0.553 |
| LVESD (mm) | 39.4 ± 9.4 | 39.6 ± 7.8 | 0.908 |
| LVEF (%) | 39.9 ± 10.4 | 42.4 ± 11.4 | 0.255 |
| RSWMA score index | 1.8 ± 0.4 | 1.7 ± 0.4 | 0.214 |
| <i>Grade of mitral regurgitation (MR)</i> | | | |
| No MR | 25 (50%) | 20(40%) | 0.422 |
| 1/4 MR | 23 (46%) | 25 (50%) | 0.842 |
| 2/4 MR | 2 (4%) | 3 (6%) | 1 |
| 3/4 MR | 0 (0%) | 2 (4%) | 0.495 |
| 4/4 MR | 0 (0%) | 0 (0%) | – |

Continuous variables are expressed as mean and standard deviation; whereas categorical variables are expressed numbers (percentage).

LVEDD indicates left ventricular end diastolic dimension; LVEF indicates left ventricular ejection fraction; LVESD indicates left ventricular end systolic dimension; PIA indicates pre-infarction angina; RSWMA indicates resting segmental wall motion abnormality.

3.3. Immediate angiographic outcome

The final TIMI flow grade of the whole cohort was TIMI 0 in 2 patients (2%), TIMI 1 in 7 patients (7%), TIMI 2 in 10 patients (10%) and TIMI 3 in 81 patients (81%). There were more patients with TIMI flow 3 in the PIA group (96% vs. 66%, $p = 0.0002$) and more with TIMI flow 1 in the no-PIA group (14% vs. 0%, $p = 0.013$) (Table 2).

The final TMP grade of the whole cohort was TMP 0 in 7 patients (7%), TMP 1 in 5 patients (5%), TMP 2 in 20 patients (20%) and TMP 3 in 68 patients (68%). There were more patients with TMP grade 0 in the no-PIA group (7% vs. 0%, $p = 0.013$) (Table 2).

3.4. Echocardiographic outcome

There were no significant differences between the two groups regarding echocardiographic measurements of LV dimensions, LVEF, resting segmental wall abnormality index and grade of mitral regurgitation (Table 3).

4. Discussion

This study provides further evidence that pre-infarction angina (PIA) is associated with better angiographic outcome in patients presenting with acute STEMI managed by PPCI and that these patients are generally more clinically stable at presentation as demonstrated by a lower Killip class compared to those not having PIA.

PIA has been shown in several studies to be associated with better long-term (5 year) clinical outcome,⁸ and significant myocardial protection in the setting of PPCI with stenting during STEMI.¹⁴ Similar findings have also been demonstrated in patients presenting with non-STEMI, showing that PIA is very frequent in such patients, and is associated with a better

prognosis, including reduced infarct size and in-hospital ventricular arrhythmias.¹⁵

Several mechanisms may explain the differences between infarctions preceded by PIA and those that are not such as opening of pre-existing coronary collaterals, accelerated reperfusion rate, reduced microvascular obstruction and ischemic preconditioning. Collaterals alone do not seem to explain the beneficial effects of pre-infarction angina, although it is difficult to completely rule out their role in the clinical setting. The possibility that PIA is not protective per se, but rather is a predictor of more rapid coronary reperfusion is still valid. It is likely that the beneficial effects of PIA are related to ischemic preconditioning as both have very similar clinical features, although a direct demonstration of this hypothesis is still lacking.^{8,16}

The effect of total ischemic time and time to first medical contact was discussed in several studies. Luz et al. performed retrospective analyses of 575 consecutive PPCI-treated patients where they divided the patients into three groups from symptom onset to reperfusion: less than 3, 3–6, and greater than 6 h. They concluded that PPCI-treated patients within 3–6 h from symptom onset had smaller infarcts if they had experienced PIA, with no benefit for those who presented less than 3 h or greater than 6 h from symptom onset.¹⁷ However, other studies showed that the benefits of PIA were mainly associated with patients who had intermediate or late reperfusion. Although myocardial damage increased with ischemic duration in patients without PIA, no such correlation was observed in those patients with PIA. Whereas infarct size was smaller in patients with PIA regardless of ischemic time, the differences were most pronounced in prolonged ischemic time, suggesting that the protective effect of PIA may last for at least 6 h. This also implies that the benefit of late PCI may be greater in patients with PIA because more myocardium can be salvaged.¹⁴ In the current study, time to first medical contact was slightly shorter in the PIA group but this did not reach statistical significance and effects on long-term outcomes were not investigated.

Reiter et al. performed a retrospective analysis of 1031 patients admitted with a first STEMI who were managed by PPCI. They concluded that the occurrence of pre-infarction angina is associated with significant myocardial protection. Patients with PIA had a 50% reduction in infarct size compared with those patients without PIA by peak creatine kinase despite having identical ischemic times and angiographic area at risk. Protective effect of pre-infarction angina was present regardless of infarct size. In patients without PIA, they observed a linear increase in infarct size with increasing ischemic time. In contrast, patients with pre-infarction angina demonstrated no correlation between ischemic time and peak CK within 6 h of ischemia. It is noteworthy that in their study they excluded all patients with visible collaterals to the infarct artery, which further implies that the protective effect of PIA is due to “preconditioning effect” rather than the presence of collaterals.¹⁴

Another study by Zhang et al. examined the impact of angina prior to STEMI on short-term clinical outcomes in patients with acute STEMI who underwent PPCI. They enrolled a total of 875 consecutive patients with STEMI who presented within 12 h of symptom onset and who underwent sirolimus-eluting stent-based PPCI. Of these patients, 292 (33.4%) had PIA. The rate of MACE at 30 days was significantly lower for patients with PIA (7.2% vs. 12.7% in the non-PIA group,

$p = 0.01$). Specifically they demonstrated that in patients with anterior MI, the rate of major adverse cardiovascular events (MACE) at 30-day follow-up was reduced for those who had PIA.¹⁸

Kosuge et al. presented data from the Japan Acute Coronary Syndrome Study on 913 patients with STEMI undergoing PPCI, pre-infarction angina was observed in 39%. Patients with pre-infarction angina and anterior STEMI had significant reductions in infarct size and improved mortality compared with those without pre-infarction angina.^{19,20}

The benefit of ischemic preconditioning evoked by PIA was also confirmed using cardiac magnetic resonance (CMR) by Lønborg et al. in their study of 200 STEMI patients. They measured myocardial area at risk within 1–7 days and final infarct size 90 ± 21 days after the STEMI. Myocardial salvage index (MSI) was calculated. Patients with PIA had a better MSI vs. those without PIA. They concluded that pre-infarction angina increases MSI in patients with STEMI supporting the theory that pre-infarction angina leads to ischemic preconditioning.²¹

However, other studies observed no clinical benefit of pre-infarction angina. Zahn et al. analyzed 774 patients STEMI from the German Myocardial Infarction Registry treated with PPCI without stenting who had ischemic durations of up to 12 h. Pre-infarction angina occurred in 69% of all patients. They observed no clinical benefit of pre-infarction angina regarding mortality or development of heart failure.²²

De Luca et al. demonstrated that pre-infarction angina did not affect infarct size among STEMI patients undergoing PPCI ($n = 430$). Infarct size was evaluated at 30 days after intervention by Tc99m sestamibi. Pre-infarction angina did not affect either the rate of post-procedural TIMI 3 flow or infarct size. Similar results were observed in sub-analyses according to infarct location, gender or ischemia time.²³

It is worth mentioning that a study performed by Lorgis et al. on 1541 patients with non-STEMI comparing patients who had PIA (defined as chest pain up to 7 days before the episode leading to admission) compared with patients without PIA found that 45% had PIA. PIA was associated with a lower creatine kinase peak, as a reflection of infarct size. Patients with PIA developed fewer ventricular arrhythmias and heart failure during the hospital stay. Overall, there was a decrease in early cardiovascular events by 26% in patients with PIA. They concluded that PIA is very frequent in patients admitted for a first non STEMI, and is associated with a better prognosis. Accordingly they stated that protecting the myocardium by ischemic or pharmacological preconditioning should not be only in STEMI, but in all types of MI.¹⁵

The variable results from such studies might be attributed to differences in the baseline clinical characteristics of the studied populations, differences in the definition of pre-infarction angina, difference in the time of presentation after the onset of chest pain, variation in the method of quantification of infarct size and the time of follow-up, as well as differences in pharmacological interventions among the various studies.

4.1. Study limitations

This study is a single center study with a limited number of patients. Moreover, long term clinical and echocardiographic follow-up were not performed.

5. Conclusions

In patients presenting with first attack of acute anterior wall STEMI managed by PPCI, the occurrence of pre-infarction angina was associated with better Killip class at presentation, better coronary collateral grade at baseline, as well as, better immediate post-procedural TIMI flow grade.

Conflicts of interest

No conflicts of interest.

Financial disclosures

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